Modern psychopharmacology is largely the story of chemical neurotransmission. To understand the actions of drugs on the brain, to grasp the impact of diseases on the central nervous system, and to interpret the behavioral consequences of psychiatric medicines, one must be fluent in the language and principles of chemical neurotransmission. The importance of this fact cannot be overstated for the student of psychopharmacology. What follows in the next two chapters will form the foundation for the entire book and the road map for a journey through one of the most exciting topics in science today: the neuroscience of how drugs and disorders act on the central nervous system.

What is neurotransmission? It can be described in many ways: anatomically, chemically, electrically. This chapter (Chapter 2) describes the anatomical basis of neurotransmission by showing how neurons are the substrates of neurotransmission and how they develop, migrate, form synapses, and demonstrate “plasticity,” or the ability to morph and change throughout life. Classically, the central nervous system has been envisioned as a series of “hard-wired” synaptic connections between neurons, not unlike millions of telephone wires within thousands upon thousands of cables. Building on the structural and functional description of neurons in Chapter 1, this chapter emphasizes what is called the anatomically addressed nervous system. The anatomically addressed brain is thus a complex wiring diagram, ferrying electrical impulses to wherever the “wire” is plugged in (i.e., at a synapse). Following this discussion, the next chapter (Chapter 3) describes the chemical basis of neurotransmission by demonstrating how chemical signals are coded, decoded, transduced, and sent along their way.
FIGURE 2-1 Time course of neurodevelopment. The time course of brain development is shown here. Most neurogenesis, neuronal selection, and neuronal migration occur before birth, although it has recently been discovered that new neurons can form in some brain areas even in adults. After birth, differentiation and myelination of neurons as well as synaptogenesis continue throughout a lifetime. Brain restructuring also occurs throughout life, but is most active during childhood and adolescence in a process known as competitive elimination.

Neurodevelopment in the anatomically addressed nervous system

Time course of neurodevelopment
Understanding of human brain development is advancing at a rapid pace. Most neurons are formed and the survivors selected by the end of the second trimester of prenatal gestation (Figures 2-1 and 2-2). Neuronal migration starts within weeks of conception and is largely complete by birth. Thus, human brain development is much more dynamic before than after birth, with the brain’s volume reaching 95% of its adult size by age 5. On the other hand, several processes affecting brain structure persist throughout a lifetime. Myelination of axon fibers and branching or arborization of neurons into their treelike structures continue vigorously at least throughout adolescence and to a lesser degree throughout life. Brain restructuring also appears to occur throughout a lifetime, but it is most active during childhood and adolescence in a process known as competitive elimination of synapses (Figures 2-1 and 2-2). After an early burst, synaptogenesis seemingly occurs steadily thereafter. Recently, it has been discovered that the formation of new neurons also continues to occur in some brain areas (Figures 2-1 through 2-4). This is remarkable, since neurogenesis until recently was thought not to occur in adult humans. Both the neuron and its synapses are
Overview of Neurodevelopment

Figure 2-2 Process of neurodevelopment. The process of brain development is shown here. After conception, stem cells differentiate into immature neurons. Those that are selected migrate and then differentiate into different types of neurons, after which synaptogenesis occurs.

Adult Neurogenesis in the Dentate Region of the Hippocampus

Figure 2-3 Neurogenesis in adult hippocampus. It was recently discovered that neurogenesis can occur in the adult brain. It occurs in two specific regions: the dentate gyrus of the hippocampus and the olfactory bulb. As shown here, neuronal precursors in the subgranular zone of the hippocampus proliferate, migrate, and differentiate into new functioning neurons.
Adult Neurogenesis in the Hippocampus

- Stress
- Depression
- Aging

- Learning
- Exercise
- Growth factors
- Antidepressants

1. Proliferation
2. Migration
3. Differentiation

FIGURE 2-4 Neurogenesis in adult hippocampus. Learning, exercise, endogenous growth factors, psychotherapy, and even antidepressants and other psychopharmacological agents can help promote adult neurogenesis in the hippocampus. On the other hand, cell loss or atrophy may occur as a result of stress, depression, and aging.

quite "plastic" – changeable and malleable – more so earlier in life but to a certain extent forever.

Neurogenesis

Neurogenesis begins after conception with embryonic stem cells differentiating into immature neurons (Figures 2-1 and 2-2). In adults, this continues from adult stem cells, but only in two evolutionarily primitive regions: the hippocampal dentate gyrus from neuronal precursors in the subgranular zone (Figure 2-3) and the olfactory bulb from neuronal precursors in the subventricular zone. The hippocampus appears to be an area of the brain that is particularly sensitive and vulnerable to the ravages of stress, aging, and disease (Figure 2-4), so it is a good thing that this site is endowed with the ability to restore itself through the production, migration, and differentiation of precursor cells into new functioning neurons (Figures 2-3 and 2-4). Neurogenesis in the hippocampus may be stimulated through learning, psychotherapy, exercise, endogenous growth factors, and even certain psychopharmacologic agents (Figure 2-4).

The loss of synapses with or without the loss of neurons could also be triggered in other areas of the brain by the same factors that affect the hippocampus, such as stress, depression, aging, and neurodegeneration (compare Figures 2-5 and 2-6). One strategy to deal with this is to promote the production of endogenous growth factors to rescue ailing neurons before they actually die, and to do this with interventions such as learning, exercise, psychotherapy, and antidepressants and other psychopharmacologic drugs (Figure 2-7).
FIGURE 2-5 Normal synaptic connection. Shown here is a normal synaptic connection allowing normal communication between two healthy neurons, with the synapse between the red and blue neuron magnified.

FIGURE 2-6 Synapse loss. Stress, depression, aging, and neurodegeneration can lead to the loss of synapses with or without the loss of neurons in any area of the brain. In contrast to the healthy neuron in Figure 2-5, the red neuron depicted here is no longer functioning to allow normal neurotransmission with the blue neuron (see box) and is about to die.
FIGURE 2-8 Transplantation of precursor stem cell. Transplantation of a precursor neuronal stem cell by neurosurgical techniques is another potential mechanism for replacing the function of a degenerated neuron. In this case, the transplanted stem cell differentiates into the turquoise neuron, which makes the same neurotransmitter that was formerly made by the red neuron (see Figure 2-5) prior to degenerating. Synaptic neurotransmission is theoretically restored when the transplanted neuron derived from the stem cell takes over the lost function of the degenerated neuron (see box). Transplantation of fetal substantia nigra cells has been performed in patients with Parkinson's disease and shown to improve motor functioning in some cases. Experimentation with the transplantation of both fetal and adult stem cells is ongoing and poses both technical and ethical issues that remain to be resolved.

FIGURE 2-7 Restoration of neurons by growth factor. This figure demonstrates how a degenerating neuron might be rescued by a growth factor. In this case, the dying neuron of Figure 2-6 is salvaged by a growth factor, which restores the function of neurotransmission to reanimate normal communication between the red neuron and the blue neuron (see box). Promotion of endogenous growth factors can be achieved through learning, exercise, psychotherapy, or psychopharmacological agents.
Neurodevelopment and neuronal selection. Neurons are formed in excess prenatally (top). Some are healthy and others may be defective. Normal neurodevelopment chooses the good neurons (left), but in a developmental disorder, some defective neurons may be chosen and thus cause a neurological or psychiatric disorder later in life when that neuron is called on to perform its duties (right).

If it is surprising that production of neurons (i.e., neurogenesis), as well as differentiation of neurons, can occur in mature human brains, it is perhaps equally shocking that — periodically throughout the life cycle and under certain specific conditions — neurons decide to kill themselves in a type of molecular hari-kari called apoptosis (Figures 2-1, 2-2, and 2-10). In fact, up to 90% of the neurons that the brain makes during fetal development commit “apoptotic suicide” before birth, particularly in some brain areas. Since the mature human brain contains approximately 100 billion neurons, whereas perhaps nearly a trillion are initially formed, this means that billions of neurons are apoptotically destroyed between conception and birth.
Necrosis and apoptosis

Neuronal death can occur by either necrosis or apoptosis. Necrosis is analogous to neuronal assassination, in which neurons, after being destroyed by poisons, suffocation, or toxins, explode and cause an inflammatory reaction. On the other hand, apoptosis is akin to neuronal suicide and results when the genetic machinery is activated to cause the neuron to literally "fade away" without causing the molecular mess of necrosis.

Why should a neuron purposely slit its own throat and commit cellular suicide? For one thing, if a neuron or its DNA gets damaged by a virus or a toxin, apoptosis destroys and silently removes these sick genes and their neurons, which may serve to protect surrounding healthy neurons. More importantly, apoptosis appears to be a natural part of development of the immature central nervous system. One of the many wonders of the brain is the built-in redundancy of neurons early in development. These neurons compete vigorously to migrate, innervate target neurons, and drink trophic factors necessary to fuel this process. Apparently there is survival of the fittest, because 50% to 90% of many types of neurons normally die at this time of brain maturation. Apoptosis is a natural mechanism to eliminate the unwanted neurons without making as big a molecular mess as would be involved in doing it via necrosis (Figure 2-10).

How do neurons kill themselves? Apoptosis is programmed into the genome of various cells, including neurons, and when activated, causes the cell to self-destruct. This is not the messy affair associated with cellular poisoning or suffocation known as necrosis.
TABLE 2-1 Some selected neurotrophic factors: an alphabet soup of brain tonics

<table>
<thead>
<tr>
<th>Factor</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>NGF</td>
<td>nerve growth factor</td>
</tr>
<tr>
<td>P75</td>
<td>proapoptotic receptors</td>
</tr>
<tr>
<td>TrkA</td>
<td>antiapoptotic receptors</td>
</tr>
<tr>
<td>GDNF</td>
<td>glial cell line-derived neurotrophic factors, which include neurturin, c-REF, and R-alpha</td>
</tr>
<tr>
<td>BDNF</td>
<td>brain-derived neurotrophic factor</td>
</tr>
<tr>
<td>NT-3, 4, and amp-5</td>
<td>neurotrophins 3, 4, and 5</td>
</tr>
<tr>
<td>CNTF</td>
<td>ciliary neurotrophic factor</td>
</tr>
<tr>
<td>IGF I and II</td>
<td>insulin-like growth factors</td>
</tr>
<tr>
<td>FGF</td>
<td>fibroblast growth factor, which comes in both acidic and basic forms</td>
</tr>
<tr>
<td>EGF</td>
<td>epidermal growth factor</td>
</tr>
</tbody>
</table>

(Nerve growth factor) (Figure 2-10). Necrotic cell death is characterized by a severe and sudden injury associated with an inflammatory response. By contrast, apoptosis is more subtle, akin to fading away. Apoptotic cells shrink, whereas necrotic cells explode (Figure 2-10). The scientists who originally discovered apoptosis coined that term to rhyme with necrosis; it also means literally a “falling off,” as the petals fall off a flower or the leaves fall from a tree. The machinery of cell death involves a set of genes that stand ever ready to cause self-destruction if activated.

Dozens of neurotrophic factors regulate the survival of neurons in the central and peripheral nervous systems (Table 2-1). A veritable alphabet soup of neurotrophic factors contributes to the brain broth of chemicals that bathe and nourish nerve cells. Some are related to nerve growth factor (NGF), others to glial cell line-derived neurotrophic factor (GDNF), and still others to various other neurotrophic factors (Table 2-1). A more comprehensive list of neurotrophins and growth factors is also given in Table 5-11. Some neurotrophic factors can trigger neurons to commit cellular suicide by making them fall on their apoptotic swords. The brain seems to choose which nerves live or die partially by whether a neurotrophic factor nourishes them or chokes them to death. That is, certain molecules (like NGF) can interact at proapoptotic “grim reaper” receptors to trigger apoptotic neuronal demise. However, if NGF decides to act on a neuroprotective “bodyguard” receptor, the neuron prospers.

Neuronal migration

Not only must the correct neurons be selected, but they must migrate to the right parts of the brain (Figures 2-1, 2-2, 2-11, and 2-12). While the brain is still under construction in utero, whole neurons wander (Figures 2-11 and 2-12). Improper migration of neurons can lead to a neurodevelopmental disorder later in life (Figure 2-12), such as epilepsy, mental retardation, psychosis, or possibly learning disabilities and various childhood-onset psychiatric disorders such as attention deficit hyperactivity disorder. Later, with the exception of those two areas of adult brain containing neuronal precursors and discussed above, only the axons of mature neurons can move.

Neurons are initially produced in the center of the developing brain. Consider that 100 billion human neurons, selected from nearly a trillion, must migrate to the right places in order to function properly. What could possibly direct all this neuronal traffic? It turns out that an amazing form of chemical communication calls forth the neurons to the right places and in the right sequences. At speeds up to 60 millionths of a meter per hour, they...
FIGURE 2-11 Neuronal migration. After neurons are selected, they must migrate to the right parts of the brain. Initially, neurons trace glial cells like a trail through the brain to their destinations. Adhesion molecules are coated on neuronal surfaces of the migrating neuron, while complementary molecules on the surface of glia allow the migrating neuron to stick there. Later, neurons can trace the axons of other neurons already in place.

FIGURE 2-12 Neuronal migration. Neurons are formed in central growth plates (top) and then migrate out into the growing brain. If this is done properly (left), the neurons are properly aligned to grow, develop, form synapses, and generally function as expected. However, if there is abnormal migration of neurons (right), the neurons are not in the correct places and do not receive the appropriate inputs from incoming axons; therefore they do not function properly. This may result in a neurological or psychiatric disorder.
neuronal cell adhesion molecules such as H-CAM, G-CAM, VCAM-1
amyloid precursor protein
Integrin
N-cadherin
Laminin
Tenacin
Proteoglycans
Heparin-binding growth-associated molecule
Glial hyaluronate-binding protein
Clusterin

TABLE 2-2 Some selected recognition molecules

<table>
<thead>
<tr>
<th>Molecule</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSA-NCAM</td>
<td>polysialic acid–neuronal cell adhesion molecule</td>
</tr>
<tr>
<td>NCAM</td>
<td>neuronal cell adhesion molecules such as H-CAM, G-CAM, VCAM-1</td>
</tr>
<tr>
<td>APP</td>
<td>amyloid precursor protein</td>
</tr>
<tr>
<td>Integrin</td>
<td></td>
</tr>
<tr>
<td>N-cadherin</td>
<td></td>
</tr>
<tr>
<td>Laminin</td>
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<tr>
<td>Tenacin</td>
<td></td>
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<tr>
<td>Proteoglycans</td>
<td></td>
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<tr>
<td>Heparin-binding growth-associated molecule</td>
<td></td>
</tr>
<tr>
<td>Glial hyaluronate-binding protein</td>
<td></td>
</tr>
<tr>
<td>Clusterin</td>
<td></td>
</tr>
</tbody>
</table>

travel to their proper destination, set up shop, and then send out their axons to connect with other neurons. These neurons know where to go because of a series of remarkable chemical signals, different from neurotransmitters, called adhesion molecules (Table 2-2). First, glial cells form a cellular matrix (Figures 2-2 and 2-11). Neurons can trace glial fibers like a trail through the brain to their destinations. Later, neurons can follow the axons of other neurons already in place and trace along the trail already blazed by the first neuron. Adhesion molecules are coated on neuronal surfaces of the migrating neuron, and complementary molecules on the surface of glia allow the migrating neuron to stick there. This forms a kind of molecular Velcro, which anchors the neuron temporarily and directs its walk along the route paved by the appropriate cell surfaces. Settlement of the brain by migrating neurons is complete by birth, but axons of neurons, upon activation, can grow for a lifetime.

**Synaptogenesis: directing the axons and arborizing the dendritic trees**

Once neurons settle down in their homesteads, their task is to form synapses. How do their axons know where to go? Neurotrophins regulate not only which neuron lives or dies but also whether an axon sprouts and which target it innervates. During development in the immature brain, neurotrophins can cause axons to cruise all over the brain, following long and complex pathways to reach their correct targets. Neurotrophins can induce neurons to sprout axons by having them form an axonal growth cone (Figures 2-13 and 2-14). Once the growth cone is formed, neurotrophins as well as other factors make various recognition molecules for the sprouting axon, presumably by having neurons and glia secrete these molecules into the chemical stew of the brain's extracellular space (Figures 2-13 and 2-14). These recognition molecules can either repel or attract growing axons, sending directions for axonal travel like a semaphore signaling a navy ship (Figure 2-13). Indeed, some of these molecules are called semaphorins to reflect this function. Once the axon growth tip reaches port, it is told to collapse by semaphorin molecules called collapsins, allowing the axon to dock into its appropriate postsynaptic slip and not sail past it (Figure 2-14). Other recognition molecules direct axons away by emitting repulsive axon guidance signals (RAGS) (Figure 2-13).

As brain development progresses, the distance that axonal growth cones can travel is greatly impeded but not completely lost. The fact that axonal growth is retained in the mature brain suggests that neurons continue to alter their targets of communication,
FIGURE 2-13 Axonal growth cones. Neurotrophins can induce neurons to sprout axons by having them form an axonal growth cone. Once the growth cone is formed, neurons or glia in the area make recognition molecules that are repulsive and cause axons to grow away from such molecules or that are attractant and encourage axonal growth toward such molecules. Neurotrophic factors thus direct axonal traffic in the brain and help determine which axons synapse with which postsynaptic targets.

FIGURE 2-14 Axonal growth cone docking. This figure depicts the axonal growth cone “docking” at its neuronal destination with the guidance of various recognition molecules.

perhaps by repairing, regenerating, and reconstructing synapses as demanded by the evolving duties of a neuron. A large number of recognition molecules supervise this. Some of these include not only semaphorins and collapsins but also molecules such as netrins, neuronal cellular adhesion molecules (NCAMs), integrins, cadherins, and cytokines (Table 2-2). When things go right, innervation proceeds smoothly and the brain is correctly “wired” (Figure 2-15). However, if there is misdirection of synaptic formation, the wrong neurons can plug into the wrong places and leave the brain with the wrong wiring (Figure 2-16). It is difficult to conceptualize how to provide therapeutic agents that could correctly redirect these neurons. One possibility is that repetition of a good behavior, learning, or psychotherapy could all have the potential to restructure and thus rehabilitate the brain over long periods of time. Certainly having the best experiences and input from the environment during neurodevelopment seems to be a desirable goal, as this may lead to the proper direction of synapses to the correct target neurons and thus lead to the development of an appropriately arborized dendritic tree (Figures 2-17, 2-18, and 2-19). On the other hand, deprivation,
FIGURE 2-15 Correct wiring of neurons. This figure represents the correct wiring of two neurons. During development, the incoming blue axons from all different parts of the brain are appropriately directed to their appropriate target dendrites on the blue neuron. Similarly, the incoming red axons from various regions of the brain are appropriately paired with their correct dendrites on the red neuron.

FIGURE 2-16 Wrong wiring of neurons. This figure represents simplistically a possible disease mechanism in neurodevelopment disorders. In this case, the neurons do not fail to develop connections, do not die, and do not degenerate. Rather, formation of the synapse is misdirected, resulting in the wrong wiring. This could lead to abnormal information transfer, confusing neuronal communications, and the inability of neurons to function; this is postulated to occur in schizophrenia, mental retardation, and other neurodevelopmental disorders. This state of chaos is represented here as a tangle of axons, where red axons inappropriately innervate blue dendrites and blue axons inappropriately pair up with red dendrites. This is in contrast to the organized state represented in Figure 2-15.
emotional or physical abuse, or bad experiences during childhood while neurons are forming their synapses could potentially be associated with inadequate (Figures 2-18 and 2-19) as well as incorrect synaptogenesis (Figure 2-16), resulting in insufficient dendritic arborization (Figure 2-19). Contemporary theories suggest that failure to form the correct synapses or a rich, prosperous portfolio of synapses may be associated with neurodevelopmental
disorders, whereas the hallmark of a neurodegenerative disorder is loss of the correct synapses once they have been developed in the right places (Figure 2-18).

**Synaptic plasticity**

Once the neurons have migrated to the right places and the axons grow into the proximity of the right dendrites, the next step is an elegant molecular structuring of the synaptic
connections themselves. Synapses can form on many parts of a neuron, not just the dendrites as axodendritic synapses, but also on the soma as axosomatic synapses, and even at the beginning and at the end of axons (axoaxonic synapses) (Figure 2-20). Such synapses are said to be "asymmetric," since communication is structurally designed to be in one direction—i.e., anterograde from the axon of the first neuron to the dendrite, soma, or axon of the second neuron (Figures 2-20 and 2-21).

This means that there are presynaptic elements that differ from postsynaptic elements (Figure 2-21). Specifically, neurotransmitter is packaged in the presynaptic nerve terminal, like ammunition in a loaded gun, and then fired at the postsynaptic neuron to target its receptors.

How do synapses form? An overview of this process is shown in Figure 2-22. Many axons, long before they make any contact with a candidate postsynaptic site, have a few of the elements involved in making molecular contacts with postsynaptic elements already in place (Figures 2-22 and 2-23). Similarly, many potential postsynaptic sites, even when no axon is nearby, also express a few of the molecules that have the potential to link with presynaptic sites (Figures 2-22 and 2-23). Each of these constitutes a rudimentary hemisynapse that is capable of making a trial contact by linking prehemisynaptic molecules with posthemisynaptic molecules when the opportunity arises—that is, when one makes physical contact with the other. If the trial contact does not work out, the connection is never strengthened and is lost. However, much like dating, if the trial contact is successful, each hemisynapse works to improve the relationship with the other. That is, each element contributes more and more molecules to the connections they share with each other, eventually forming a fully functioning synapse (Figure 2-22).

Specifically, many specialized molecular components must be assembled to form a fully functional synapse from two rudimentary hemisynapses. These components are derived either from preformed supplies that are already waiting in an axon terminal's hemisynapse or a dendritic spine's hemisynapse or from newly synthesized synaptic molecules that are ordered by each hemisynapse chemically signaling its own genome, back in its corresponding cell nucleus, to make and then ship the necessary supplies to the site of the emerging synapse.

Just like a construction site, the area of new synapse formation is abuzz with activity, from ramping up the synthesis and delivery of supplies of some very specific proteins that are needed on each side of the synapse to actually erecting them into a structural and functional unit. Both pre- and postsynaptic hemisynapses contribute CAMs (cellular adhesion molecules) to their extracellular contact site, thus providing a type of "molecular glue" that solidifies the structural link they share (Figure 2-25 and Table 2-2). Both elements also need intracellular scaffolding proteins such as actin, the same protein that is in skeletal muscle, to support the shape and strength of the emerging pre- and postsynaptic elements (Figure 2-26). The presynaptic side needs some very specialized materials that are not present in the postsynaptic element, such as synaptic vesicles full of neurotransmitters, synthetic and catabolic enzymes, reuptake transporters, ion channels, and specialized proteins that constitute the active zone allowing neurotransmitter release (Figure 2-27). The postsynaptic side also requires specialized proteins not present on the presynaptic side, such as postsynaptic receptors matched to the neurotransmitter being used by the presynaptic neuron, signal cascade molecules, and specialized proteins constituting the postsynaptic density that allows signal detection from the presynaptic neuron (Figure 2-27).

Once the synapse is formed, it remains a dynamic area of intense molecular activity. In other words, the construction crew that ordered, manufactured, and received the shipped supplies of molecules and then assembled them into a working synapse are not dismissed as
FIGURE 2-20 Axodendritic, axosomatic, and axoaxonic connections. After neurons migrate, they form synapses. As shown in this figure, synaptic connections can form not just between the axon and dendrites of two neurons (axodendritic) but also between the axon and the soma (axosomatic) or the axons of the two neurons (axoaxonic). Communication is anterograde from the axon of the first neuron to the dendrite, soma, or axon of the second neuron.
FIGURE 2-21 Enlarged synapse. The synapse is enlarged conceptually here showing the specialized structures that enable chemical neurotransmission to occur. Specifically, a presynaptic neuron sends its axon terminal to form a synapse with a postsynaptic neuron. Energy for neurotransmission from the presynaptic neuron is provided by mitochondria there. Chemical neurotransmitters are stored in small vesicles, ready for release upon firing of the presynaptic neuron. The synaptic cleft is the gap between the presynaptic neuron and the postsynaptic neuron; it contains proteins and scaffolding and molecular forms of "synaptic glue" to reinforce the connection between the neurons. Receptors are present on both sides of this cleft and are key elements of chemical neurotransmission.

soon as the synapse is functional. In many ways, a synapse is under constant revision as long as it is functional, with molecular maintenance and alterations constantly instituted to respond to changing conditions and its amount of use by the neurons it connects. For example, it has been said that "neurons that fire together wire together," and this is demonstrated not only by the construction of the synapse, shown in Figures 2-22 through 2-27, but also in the molecular changes shown in Figures 2-28 through 2-31. For example, as more neurotransmitter is released, it can change the number of pre- and postsynaptic receptors expressed at that synapse as well as the richness of the pre- and postsynaptic densities seen at the synapse (Figure 2-28). This presumably reflects adaptive molecular and structural changes that facilitate the ease of neurotransmission. Sometimes the changes instituted at a synapse in response to high degrees of utilization are not only on the molecular level but can lead to dramatic physical and structural alterations in the synapse. For example, the surface areas of both pre- and postsynaptic faces can increase, presumably to accommodate enriched
Overview of Formation of a Synapse

FIGURE 2-22 Synapse formation. This figure summarizes the process of synapse formation, which is depicted in more detail in Figures 2-23 through 2-27. Most pre- and postsynaptic sites already have some of the elements necessary for synaptic connections prior to physical contact; this is called a hemisynapse and allows the pre- and postsynaptic sites to make a trial contact with one another. In many cases, after trial contact, additional specialized molecular components are transported to the pre- and/or postsynaptic sites and assembled to form a fully functioning synapse.

FIGURE 2-23 Formation of a synapse: trial contact. Formation of a synapse, part 1. Many presynaptic axons contain some of the molecular components necessary to form a synaptic connection even before making contact with a postsynaptic site; the same is true of postsynaptic sites (in this case, the site of a dendrite). Presynaptically, this is called a hemipresynapse, while postsynaptically it is called a hemipostsynapse. The pre- and postsynaptic sites are able to make a trial contact with one another by linking hemipresynaptic molecules with hemipostsynaptic molecules.
Formation of a Synapse
Part 2: Ordering the Supplies

FIGURE 2-24 Formation of a synapse: ordering supplies. Formation of a synapse, part 2. In some cases, preformed molecular components needed to assemble a functioning synapse are already present in the pre- and posthemisynapses. In many cases, however, these supplies need to be ordered – that is, the hemisynapse signals the genome to synthesize and transport synaptic molecules to the emerging synapse.
numbers and types of receptors that facilitate communication (Figure 2-29). Vigorous presynaptic messaging can also increase the postsynaptic response by inducing the formation of an entirely separate and adjacent postsynaptic structural element (Figure 2-30). Similarly, a postsynaptic hemisynapse in the area of a presynaptic neuron may be able to receive information from that neuron, initially by spillover of its neurotransmitter directed at a neighboring postsynaptic element. Over time, however, this arrangement can induce the sprouting of an axon collateral to construct a proper, fully functioning synapse (Figure 2-31).

**Competitive elimination of synapses**

After all of this elegant effort to create synapses, it may be surprising to learn that the neuron is equipped with mechanisms to eliminate synapses as well. Interestingly, more synapses are present in the brain by age 6 than at any other time in the life cycle (Figures 2-1 and 2-2).
Formation of a Synapse
Part 4: Erecting the Intraneuronal Scaffolding

![Formation of a Synapse](image)

**FIGURE 2-26 Formation of a synapse: intraneuronal scaffolding.** Formation of a synapse, part 4. Another element needed by both the pre- and postsynapses for the formation of a functioning synapse is intracellular scaffolding protein (e.g., actin, the protein present in skeletal muscle). Actin and other intracellular scaffolding proteins help form the shape and strength of the emerging pre- and postsynaptic elements.

During the next 5 to 10 years and into adolescence, the brain systematically removes half of all synaptic connections present at age 6. This still leaves about 100 trillion synapses—up to 10,000 individual synapses for some neurons—and a massively restructured brain. At a lower level of activity, this same elimination of synapses (as well as formation of synapses) occurs over a lifetime.

How does the neuron eliminate synapses? Excitotoxicity may be the mechanism that mediates the pruning of synaptic connections. That is, just like a good gardener, the brain needs a mechanism to “prune” its dendritic tree of old, malfunctioning or unneeded synapses (Figure 2-32). Limited loss of synapses can provide a useful maintenance function. However, it is possible that this same mechanism gets turned on inappropriately or goes out of control in certain disease states (Figure 2-33) associated with excessive loss of synapses or even loss of neurons themselves (Figures 2-34 through 2-37).

Excitatory neurotransmission via the ubiquitous excitatory neurotransmitter glutamate is part of normal brain functioning; many key neurons utilize glutamate as their neurotransmitter and essentially all neurons can be excited by this neurotransmitter (Figure 2-34).
FIGURE 2-27 Formation of a synapse: decorating. Formation of a synapse, part 5. Some elements needed to form a synapse are unique to either the pre- or posthemisynapse. The prehemisynapse requires synaptic vesicles, neurotransmitters, synthetic and catabolic enzymes, reuptake transporters, ion channels, snare proteins, and other proteins that constitute the presynaptic density, which allows neurotransmitter release. The posthemisynapse requires postsynaptic receptors, signal cascade molecules, and specialized proteins constituting the postsynaptic density, which allows signal detection.

Hypothetically, some states of "overexcitation" may result in excessive excitatory neurotransmission and thus excessive neuronal activity in certain neuronal circuits. This process is theoretically associated with unwanted psychiatric or neurologic symptoms, such as panic, pain, or even a seizure (Figure 2-35). Following such a barrage of excessive excitatory neurotransmission and the associated symptoms, the brain may experience damage to the very synapses that mediated this process, to the point where parts of dendrites of the affected neurons are destroyed (Figure 2-36). Even greater degrees of excitation may hypothetically destroy entire neurons in some neurodegenerative conditions, such as schizophrenia (Figure 2-37). Thus, normal but limited excitotoxicity may be useful for routine pruning of neurons, but excitotoxicity run amok may be a mechanism for unwanted symptoms and even brain damage in certain pathological conditions.
During neurodevelopment, perhaps some process like excitotoxicity is turned on in order to effect the dramatic restructuring of the brain that occurs in late childhood and adolescence (Figure 2-38). If all goes well, neurodevelopmental experiences and genetic programming will lead the brain to select wisely which connections to keep and which to destroy. Done appropriately, the individual prospers during this maturational task and advances gracefully into adulthood. Bad selections theoretically could lead to neurodevelopmental disorders such as schizophrenia or attention deficit hyperactivity disorder.

The growth of new synapses and the pruning of old synapses then proceeds throughout a lifetime, but at a much slower pace and over shorter distances than in earlier in development. Thus the axons and dendrites of each neuron are constantly changing, establishing new connections and removing old ones. The brain never really stops developing; it only slows down. After dramatically reducing neurons before birth and then synapses during late childhood and early adolescence, this process calms down considerably in the mature brain, where maintenance and remodeling of synapses continue in modest amounts and over more limited distances. Although the continuous structural remodeling of synapses in the mature brain, directed by recognition molecules, cannot approximate the pronounced long-range growth of early brain development, this restriction can be beneficial, in part because it...
Postsynaptic Structural Changes with Long-Term Potentiation and Synaptic Activity

FIGURE 2-30 Formation of separate and adjacent postsynaptic site. Postsynaptic structural changes that can occur with long-term potentiation and synaptic activity are shown here. Increased neurotransmission may lead to an increased number of postsynaptic receptors (panel 2) as well as increased surface area of the postsynaptic face (panel 3), which may ultimately induce the formation of a separate and adjacent postsynaptic site (panels 4 and 5).

Presynaptic Structural Changes with Long-Term Potentiation and Synaptic Activity

FIGURE 2-31 Formation of new functioning synapse. Presynaptic structural changes that can occur with long-term potentiation and synaptic activity are shown here. Formation of a new posthemisynapse (panels 1 and 2) may eventually lead to the formation of an axon collateral (panel 3) to construct a fully functioning synapse (panel 4).

simultaneously allows structural plasticity while restricting unwanted axonal growth. This would stabilize brain function in the adult and could, furthermore, prevent chaotic rewiring of the brain by limiting both axonal growth away from appropriate targets and ingrowth from inappropriate neurons. On the other hand, the price of such growth specificity becomes apparent when a long-distance neuron in the adult brain dies, thus making it difficult to reestablish original synaptic connections even if axonal growth is turned on.

As previously discussed, neurons and their supportive and neighboring glia elaborate a rich array of neurotrophic factors that either promote or eliminate synaptic connections. The potential for releasing growth factors is preserved forever, which contributes to the possibility of constant synaptic revision throughout the life of that neuron. Such potential changes in synaptogenesis may provide the substrate for learning, emotional maturity, and the development of cognitive and motor skills throughout life. However, it is not clear how the brain dispenses its neurotrophic factors endogenously during normal adult physiological functioning. Presumably, demand to use neurons is met by keeping them fit and ready to function – a task accomplished by salting the brain broth with neurotrophic factors that keep the neurons healthy. Perhaps thinking and learning provoke the release of neurotrophic factors. Maybe “use it or lose it” applies to adult neurons, with neurons being preserved and new connections being formed if the brain stays active. It is even possible that the brain could lose its “strength” in the absence of “mental exercise.” Perhaps inactivity leads to pruning of unused, “rusty” synapses, even triggering apoptotic demise of entire inactive neurons. On
Dendrites in need of "pruning"

FIGURE 2-32 Normal dendritic pruning. The dendritic tree of a neuron not only sprouts branches, grows, and establishes a multitude of new synaptic connections throughout its life but can also remove, alter, trim, or destroy such connections when necessary. The process of dismantling synapses and dendrites may be controlled by removal of growth factors or by a naturally occurring destructive process sometimes called excitotoxicity. Thus, there is a normal "pruning" process for removing dendrites.

"Pruning" out of control

A disease may let the normal process of pruning get out of control. The disease can cause the neuron to be "pruned to death."

FIGURE 2-33 Out of control dendritic pruning. Neurons appear to have a normal maintenance mechanism for their dendritic tree by which they are able to prune or remove old, unused, or useless synapses and dendrites (shown in Figure 2-32). One postulated mechanism for some degenerative diseases is that this otherwise normal pruning mechanism may get out of control, eventually rendering the neuron useless or killing it by pruning it to death.
Glutamate opens the ion channel, allowing calcium to enter the cell. 

**FIGURE 2-34 Glutamate opens the calcium channel.** Shown here are details of calcium entering a dendrite of the blue neuron when the red neuron excites it with glutamate during normal excitatory neurotransmission. Glutamate released from the red neuron travels across the synapse, docks into its agonist slot on its receptor, and, as ionic gatekeeper, opens the calcium channel to allow calcium to enter the postsynaptic dendrite of the blue neuron to mediate normal excitatory neurotransmission (see box).

**FIGURE 2-35 Too much neurotransmission can lead to symptoms.** Shown here is what may happen when excitatory neurotransmission causes too much neurotransmission. This may possibly occur during the production of various symptoms mediated by the brain, including panic attacks. It could also occur during mania, positive symptoms of psychosis, seizures, and other neuronally mediated disease symptoms. In this case, too much glutamate is being released by the red neuron, causing too much excitation of the postsynaptic blue neuron's dendrite. Extra release of glutamate causes additional occupancy of postsynaptic glutamate receptors, opening more calcium channels and allowing more calcium to enter the blue dendrite (see box). Although this degree of excessive neurotransmission may be associated with psychiatric symptoms, it does not necessarily damage the neuron.
FIGURE 2-36 Too much neurotransmission can lead to dendritic death. If too much neurotransmission occurs for too long, it is hypothetically possible that this would lead to dendritic death. The mechanism for this may be tantamount to inappropriately activating the normal dendritic pruning process. Thus, far too much glutamate release can cause too much opening of the gates of the calcium channel, activating an excitotoxic demise of the dendrite (see box).

FIGURE 2-37 Too much neurotransmission can lead to cell death. Catastrophic overexcitation can theoretically lead to so much calcium flux into a neuron due to dangerous, wide-range opening of calcium channels by glutamate (see box) that not only the dendrite is destroyed but also the entire neuron. This scenario is one in which the neuron is literally "excited to death." Excitotoxicity is a major current hypothesis to explain the mechanism of neuronal death in neurodegenerative disorders, including aspects of schizophrenia, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, and ischemic cell damage from stroke.
FIGURE 2-38 Synapse formation by age. Synapses are formed at a furious rate between birth and age 6. Competitive elimination and restructuring of synapses peaks during pubescence and adolescence, leaving about half to two-thirds of the synapses present in childhood to survive into adulthood.

the other hand, mental stimulation might prevent this, and psychotherapy may even induce neurotrophic factors to preserve critical cells and innervate new therapeutic targets leading to the alteration of emotions and behaviors. Only future research will clarify how to use drugs and psychotherapy to balance the seasonings in the tender stew of the brain.

Summary

The reader should now appreciate that synaptic neurotransmission is the foundation of psychopharmacology. Here we have described the “hard wiring” that supports chemical neurotransmission as the anatomically addressed nervous system. We have shown how neurons are formed, differentiate, migrate, are selected, and then form synapses. We have pointed out how normal functioning can go awry and cause neurodevelopmental or neurodegenerative disorders. The brain’s neurons are largely selected before birth and its synapses by adolescence, but new neurons and new synapses are formed (and eliminated) at lower rates throughout life. Thus, the anatomically addressed nervous system, the structural substrate for synaptic neurotransmission as well as for psychiatric disorders and drug actions, is plastic, changing, and malleable. Coupling an understanding of concepts on the anatomical basis of normal synaptic neurotransmission described here, in Chapter 2, with knowledge about the chemical basis of normal neurotransmission discussed in Chapter 3 will lead to mastery of the many modern hypotheses underlying the biological basis of psychiatric disorders and their treatments, as described throughout the rest of this book.